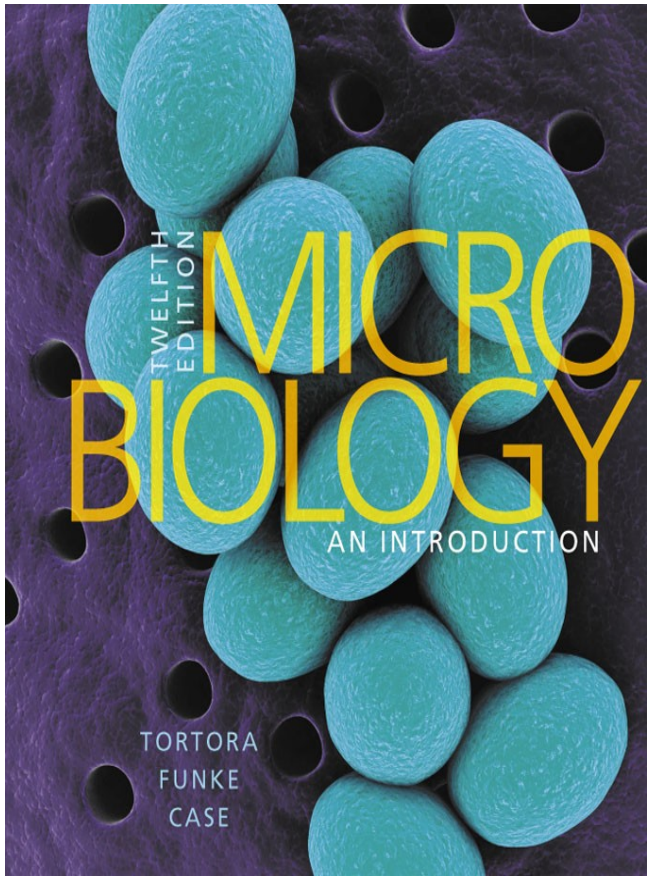
Microbiology an Introduction

Twelfth Edition

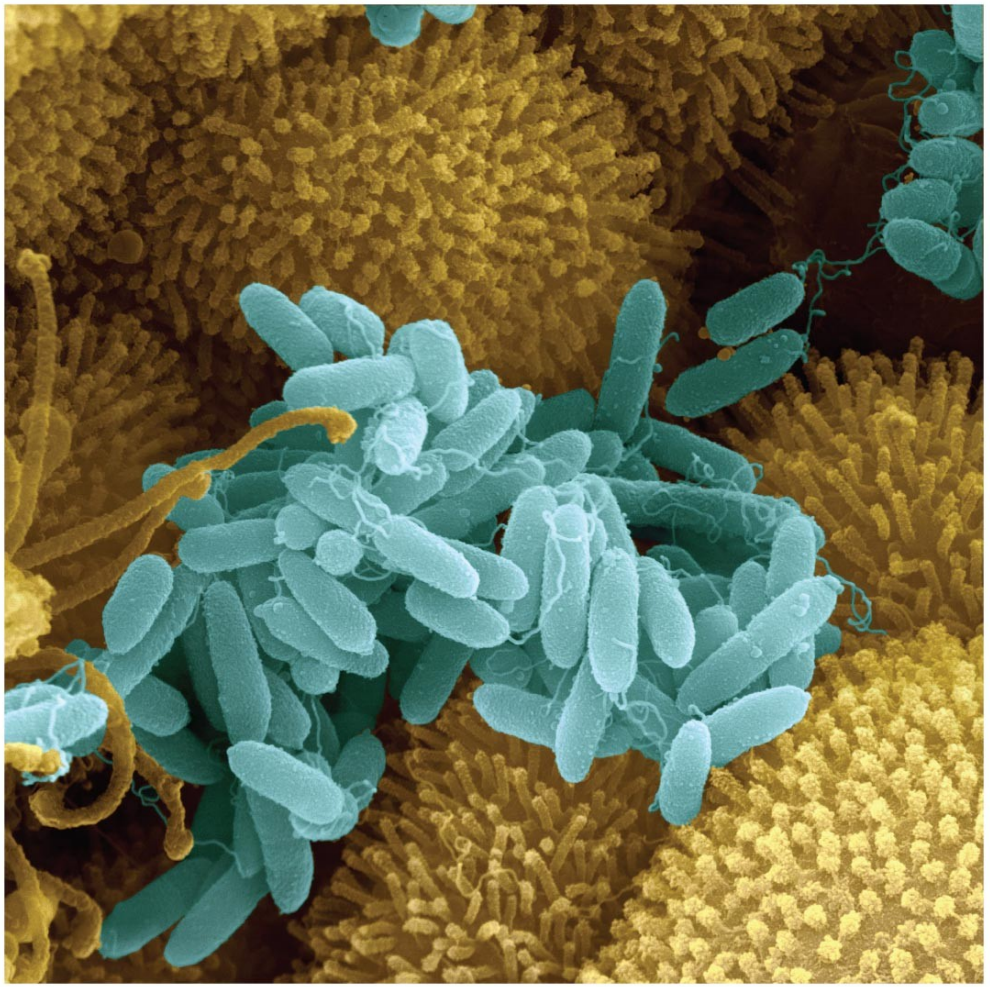


Chapter 20

Antimicrobial Drugs

Pearson

Pseudomonas Aeruginosa (Blue)



The History of Chemotherapy (1 of 3)

Learning Objectives

20-1 Identify the contributions of Paul Ehrlich and Alexander Fleming to chemotherapy.

20-2 Name the microbes that produce most antibiotics.

The History of Chemotherapy (2 of 3)

- **Selective toxicity:** selectively finding and destroying pathogens without damaging the host
- **Chemotherapy:** the use of chemicals to treat a disease
- **Antibiotic:** a substance produced by a microbe that, in small amounts, inhibits another microbe
- **Antimicrobial drugs:** synthetic substances that interfere with the growth of microbes

The History of Chemotherapy (3 of 3)

- 1928: Fleming discovered penicillin, produced by **Penicillium**
- 1932: Prontosil red dye used for streptococcal infections
- 1940: First clinical trials of penicillin
- Today there is a growing problem of antibiotic resistance

Figure 20.1 Laboratory Observation of Antibiosis

Table 20.1 Representative Sources of Antibiotics (1 of 2)

TABLE 20.1 Representative Sources of Antibiotics

Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Paenibacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Saccharopolyspora erythraea	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpurea	Gentamicin

Table 20.1 Representative Sources of Antibiotics (2 of 2)

Microorganism	Antibiotic
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium chrysogenum	Penicillin

Check Your Understanding-1

Check Your Understanding

- ✓ Who coined the term **chemotherapy**?
  20-1
- ✓ More than half our antibiotics are produced by a certain genus of bacteria. What is it?
  20-2

Spectrum of Antimicrobial Activity (1 of 2)

Learning Objectives

20-3 Describe the problems of chemotherapy for viral, fungal, protozoan, and helminthic infections.

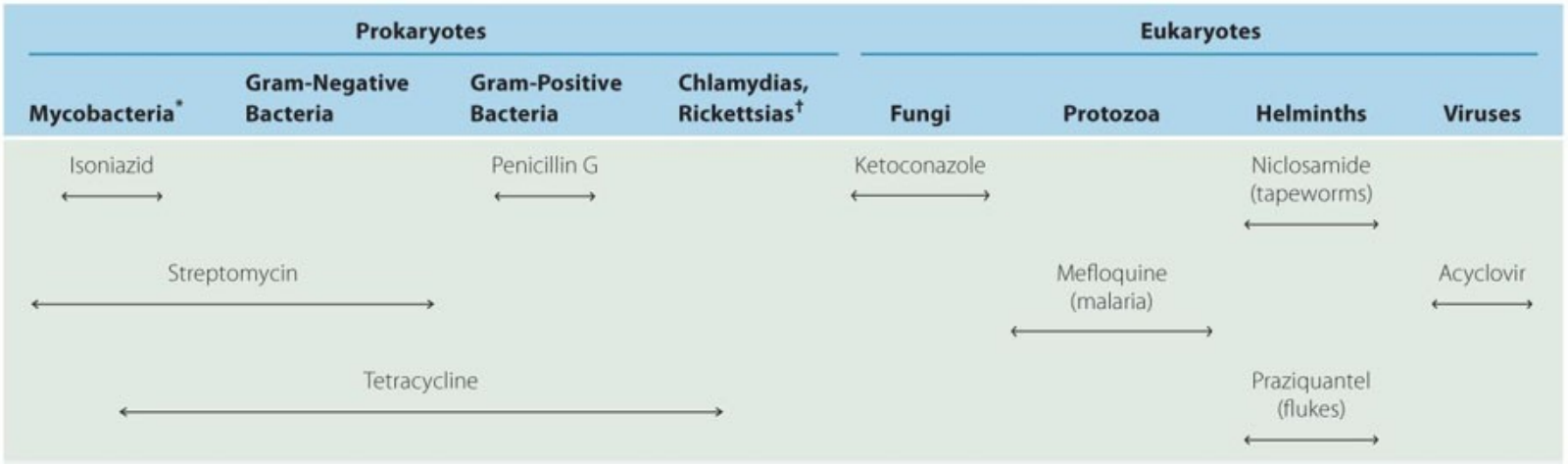
20-4 Define the following terms: **spectrum of activity, broad-spectrum antibiotic, superinfection**.

Spectrum of Antimicrobial Activity (2 of 2)

- **Narrow spectrum of microbial activity:** drugs that affect a narrow range of microbial types
- **Broad-spectrum antibiotics:** affect a broad range of gram-positive or gram-negative bacteria
- **Superinfection:** overgrowth of normal microbiota that is resistant to antibiotics

Table 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs

Table 20.2 The Spectrum of Activity of Antibiotics and Other Antimicrobial Drugs



*Growth of these bacteria frequently occurs within macrophages or tissue structures.

†Obligately intracellular bacteria.

Check Your Understanding-2

Check Your Understanding

- ✓ Identify at least one reason why it's so difficult to target a pathogenic virus without damaging the host's cells.
  20-3
- ✓ Why are antibiotics with a very broad spectrum of activity not as useful as one might first think?
  20-4

The Action of Antimicrobial Drugs (1 of 6)

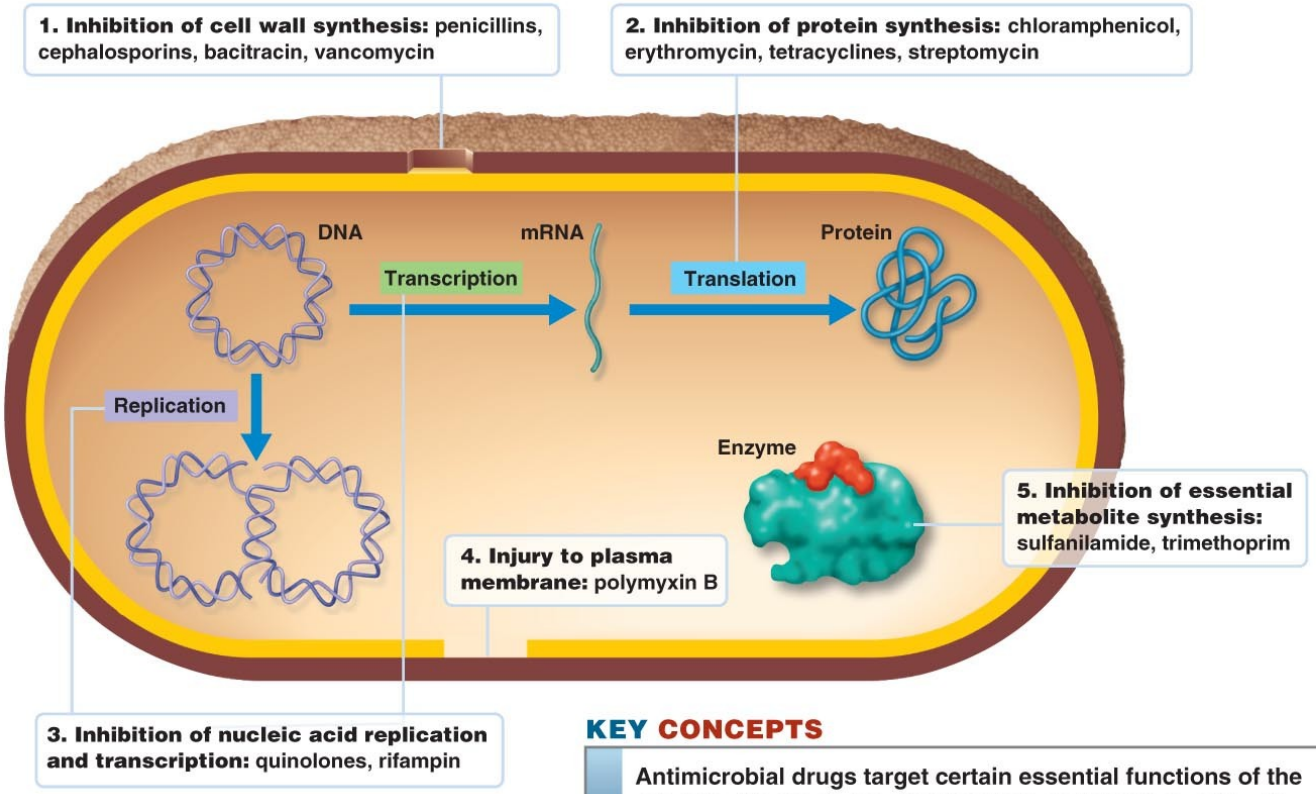
Learning Objective

20-5 Identify five modes of action of antimicrobial drugs.

The Action of Antimicrobial Drugs (2 of 6)

- **Bactericidal**
  - Kill microbes directly
- **Bacteriostatic**
  - Prevent microbes from growing

Figure 20.2 Major Action Modes of Antibacterial Drugs



KEY CONCEPTS

Antimicrobial drugs target certain essential functions of the microbe. Mechanisms of action include inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid synthesis, injuring the plasma membrane, or inhibiting synthesis of essential metabolites.

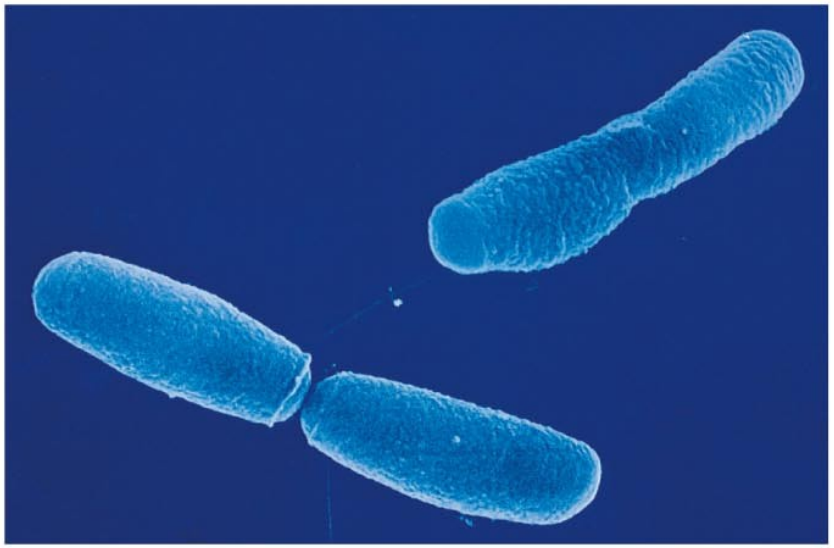
The antimicrobial drug must not interfere with essential functions of the microbe's host.

Pearson

The Action of Antimicrobial Drugs (3 of 6)

- Inhibiting cell wall synthesis
  - Penicillins prevent the synthesis of peptidoglycan

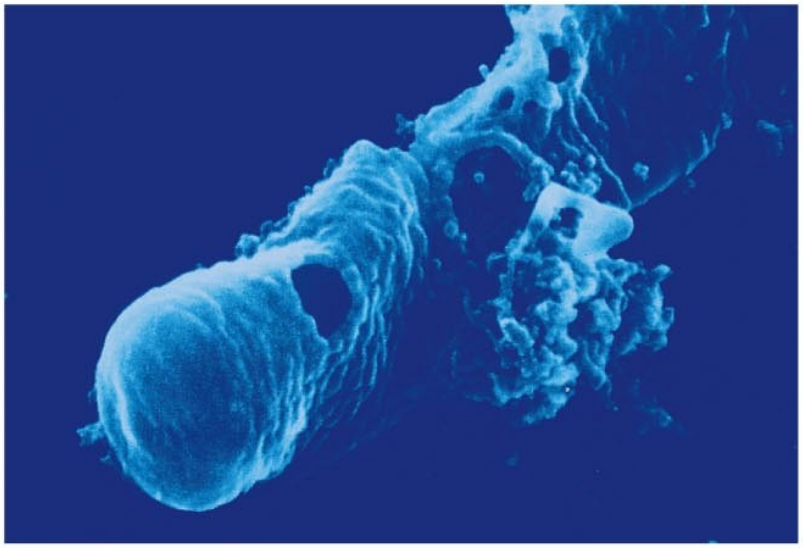
Figure 20.3 The inhibition of bacterial cell wall synthesis by penicillin



(a) Rod-shaped bacterium before penicillin

SEM

1 μm



(b) The bacterial cell lysing as penicillin weakens the cell wall

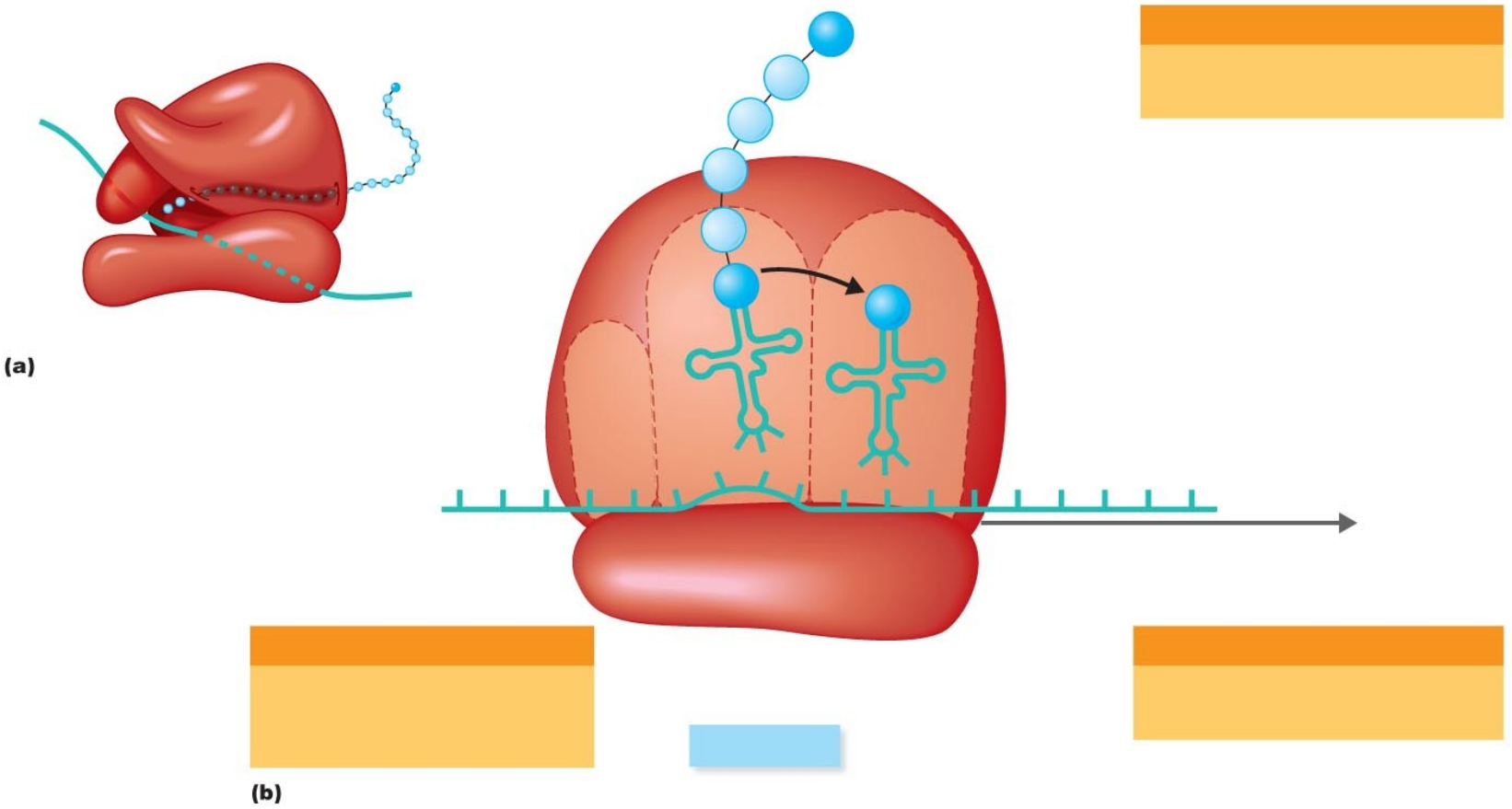
SEM

1 μm

The Action of Antimicrobial Drugs (4 of 6)

- Inhibiting protein synthesis
  - Target bacterial 70S ribosomes
  - Chloramphenicol, erythromycin, streptomycin, tetracyclines

Figure 20.4 The Inhibition of Protein Synthesis by Antibiotics



The Action of Antimicrobial Drugs (5 of 6)

- Injuring the plasma membrane
  - Polypeptide antibiotics change membrane permeability
  - Antifungal drugs combine with membrane sterols

Figure 20.5 Injury to the Plasma Membrane of a Yeast Cell Caused by an Antifungal Drug

The Action of Antimicrobial Drugs (6 of 6)

- Inhibiting nucleic acid synthesis
  - Interfere with DNA replication and transcription
- Inhibiting the synthesis of essential metabolites
  - Antimetabolites compete with normal substrates for an enzyme
    - Sulfanilamide competes with **para-aminobenzoic acid (PABA),** stopping the synthesis of folic acid

Check Your Understanding-3

Check Your Understanding

- ✓ What cellular function is inhibited by tetracyclines?

  20-5

Chemotherapeutic Agents: Modes of Action

Animation: Chemotherapeutic Agents: Modes of Action

Common Antimicrobial Drugs (1 of 3)

Learning Objectives

20-6 Explain why drugs in this section are bacteria-specific.

20-7 List the advantages of each of the following over penicillin: semisynthetic penicillins, cephalosporins, and vancomycin.

20-8 Explain why isoniazid and ethambutol are antimycobacterial agents.

Common Antimicrobial Drugs (2 of 3)

Learning Objectives

20-9 Describe how each of the following inhibits protein synthesis: aminoglycosides, tetracyclines, chloramphenicol, macrolides.

20-10 Compare polymyxin B, bacitracin, and neomycin in their modes of action.

20-11 Describe how rifamycins and quinolones kill bacteria.

20-12 Describe how sulfa drugs inhibit microbial growth.

Common Antimicrobial Drugs (3 of 3)

Learning Objectives

20-13 Explain modes of action of current antifungal drugs.

20-14 Explain modes of action of current antiviral drugs.

20-15 Explain modes of action of current antiprotozoan and antihelminthic drugs.

Table 20.3 Antibacterial Drugs
(1 of 5)

Drugs by Mode of Action	Comments
Inhibitors of Cell Wall Synthesis	
Natural Penicillins	
Penicillin G	Against gram-positive bacteria, requires injection
Penicillin V	Against gram-positive bacteria, oral administration
Semisynthetic Penicillins	
Oxacillin	Resistant to penicillinase
Ampicillin	Broad spectrum
Amoxicillin	Broad spectrum; combined with inhibitor of penicillinase
Aztreonam	A monobactam; effective against gram-negative bacteria, including **Pseudomonas** spp.
Imipenem	A carbapenem; very broad spectrum
Cephalosporins	
Cephalothin	First-generation cephalosporin; activity similar to penicillin; requires injection
Cefixime	Fourth-generation cephalosporin; oral administration

Table 20.3 Antibacterial Drugs
(2 of 5)

Drugs by Mode of Action	Comments
Inhibitors of Cell Wall Synthesis	
Polypeptide Antibiotics	
Bacitracin	Against gram-positive bacteria; topical application
Vancomycin	A glycopeptide type; penicillinase-resistant; against gram-positive bacteria
Antimycobacterial Antibiotics	
Isoniazid	Inhibits synthesis of mycolic acid component of cell wall of **Mycobacterium** spp.
Ethambutol	Inhibits incorporation of mycolic acid into cell wall of **Mycobacterium** spp.

Table 20.3 Antibacterial Drugs
(3 of 5)

Drugs by Mode of Action	Comments
Inhibitors of Protein Synthesis	
Chloramphenicol	Broad spectrum, potentially toxic
Aminoglycosides	
Streptomycin	Broad spectrum, including mycobacteria
Neomycin	Topical use, broad spectrum
Gentamicin	Broad spectrum, including *Pseudomonas* spp.
Pleuromutilins	
Mutilin, retpamulin	Inhibit gram-positive bacteria
Tetracyclines	
Tetracycline, oxytetracycline, chlortetracycline	Broad spectrum, including chlamydias and rickettsias; animal feed additives

Table 20.3 Antibacterial Drugs (4 of 5)

Drugs by Mode of Action	Comments
Inhibitors of Protein Synthesis	
Macrolides	Alternative to penicillin
Erythromycin	Semisynthetic; broader spectrum and better tissue penetration than erythromycin
Azithromycin, clarithromycin	New generation of semisynthetic macrolides; used to cope with resistance to other macrolides
Telithromycin (Ketek)	
Streptogramins	
Quinupristin and dalfopristin (Synercid)	Alternative for treating vancomycin-resistant gram-positive bacteria
Oxazolidinones	
Linezolid (Zyvox)	Useful primarily against penicillin-resistant gram-positive bacteria
Glycylcyclines	
Tygecycline	Broad spectrum, especially MRSA and **Acinetobacter**

Table 20.3 Antibacterial Drugs (5 of 5)

Drugs by Mode of Action	Comments
Injury to the Plasma Membrane	
Polymyxin B	Topical use, gram-negative bacteria, including **Pseudomonas** spp.
Lipopeptides	
Daptomycin	To treat MRSA infections
Inhibitors of Nucleic Acid Synthesis	
Rifamycins	
Rifampin	Inhibits synthesis of mRNA; treatment of tuberculosis
Quinolones and Fluoroquinolones	
Nalidixic acid, nofloxacin, ciprofloxacin	Inhibit DNA synthesis; broad spectrum; urinary tract infections
Gatifloxacin	Newest generation quinolone; increased potency against gram-positive bacteria
Competitive Inhibitors of the Synthesis of Essential Metabolites	
Sulfonamides	
Trimethoprim-sulfamethoxazole	Broad spectrum; combination is widely used

Table 20.4 Differential Grouping of Cephalosporins

Table 20.4 Differential Grouping of Cephalosporins

Generation	Description	Example
First	Relatively narrow level of activity, primarily against gram-negative bacteria	Cephalothin
Second	More extended gram-negative spectrum	Cefamdole (IV) Cefaclor (oral)
Third	Most active against gram-negative bacteria, including some pseudomonads; must be injected	Ceftazidime
Fourth	Require injections; most extended spectrum of activity	Cefepime

Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (1 of 5)

Table 20.5 Antifungal, Antiviral, Antiprotozoan, and

	Mode of Action	Comments
Antifungal Drugs		
Agents Affecting Fungal Sterols (Plasma Membrane)		
Polyenes		
Amphotericin B	Injury to plasma membrane	Systemic fungal infections; fungicidal
Azoles		
Clotrimazole, miconazole	Inhibit synthesis of plasma membrane	Topical use
Ketoconazole	Inhibits synthesis of plasma membrane	Can be taken orally for systemic fungal infections
Allylamines		
Terbinafine, naftifine	Inhibit synthesis of plasma membrane	Treatment of diseases resistant to azoles

Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (2 of 5)

	Mode of Action	Comments
Agents Affecting Fungal Cell Walls		
Echinocandins		
Caspofungin (Cancidas)	Inhibits synthesis of cell wall	Intravenous use only
Agents Inhibiting Nucleic Acids		
Flucytosine	Inhibits RNA synthesis	Usually in combination with other antifungals
Other Antifungal Drugs		
Griseofulvin	Inhibition of mitotic microtubules	Fungal infections of the skin
Tolnaftate	Unknown	Athlete’s foot

Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (3 of 5)

	Mode of Action	Comments
Antiviral Drugs		
Entry and Fusion Inhibitors		
Maraviroc	Binds CCR5	Treatment of HIV
Zanamivir, oseltamivir	Inhibit neuraminidase on influenza virus	Treatment of influenza
Uncoating Inhibitors		
Amantadine, zimantadine	Inhibit uncoating	Treatment of influenza
Genome Integration and Nucleic Acid Synthesis Inhibitors		
Zidovudine (AZT)	Inhibits DNA or RNA synthesis	Used primarily against HIV
Acyclovir, ganciclovir, ribavirin, lamivudine	Inhibit DNA or RNA synthesis	Used primarily against herpesviruses
Cidofovir	Inhibits DNA or RNA synthesis	Cytomegalovirus infections; possibly effective against smallpox
Adefovir dipivoxil (Hepsera)	Competitive inhibitor for HBV reverse transcriptase	Treatment of lamivudine-resistant infections

Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (4 of 5)

	Mode of Action	Comments
Assembly and Exit Inhibitors		
Saquinavir	Protease inhibitor	Treatment of HIV
Boceprevir	Protease inhibitor	Treatment of hepatitis C
Zanamivir, oseltamivir	Neuraminidase inhibitor	Treatment of influenza
Interferons		
Alpha interferon	Inhibits spread of virus to new cells	Viral hepatitis
Antiprotozoan Drugs		
Chloroquine	Inhibits DNA synthesis	Malaria; effective against red blood cell stage only
Diiodohydroxyquin	Unknown	Amebic infections; amebicidal
Metronidazole, tinidazole	Interfere with anaerobic metabolism	Giardiasis, amebiasis, trichomoniasis

Table 20.5 Antifungal, Antiviral, Antiprotozoan, and Antihelminthic Drugs (5 of 5)

	Mode of Action	Comments
Antihelminthic Drugs		
Niclosamide	Prevents ATP generation in mitochondria	Tapeworm infections; kills tapeworms
Praziquantel	Alters permeability of plasma membranes	Tapeworm and fluke infections; kills flatworms
Pyrantel pamoate	Neuromuscular block	Intestinal roundworms; kills roundworms
Mebendazole, albendazole	Inhibit absorption of nutrients	Intestinal roundworms
Ivermectin	Paralyzes worm	Intestinal roundworms primarily; occasional use for scabies mite and lice

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis (1 of 2)

- **Penicillin**
  - Contain a β-lactam ring
    - Types are differentiated by the chemical side chains attached to the ring
  - Prevent the cross-linking of peptidoglycans, interfering with cell wall construction (especially gram-positives)

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis (2 of 2)

- **Natural penicillins**
  - Extracted from **Penicillium** cultures
    - Penicillin G (injected) and Penicillin V (oral)
  - Narrow spectrum of activity
  - Susceptible to penicillinases (β-lactamases)
- **Semisynthetic penicillins**
  - Contain chemically added side chains, making them resistant to penicillinases

Figure 20.6a The Structure of Penicillins, Antibacterial Antibiotics

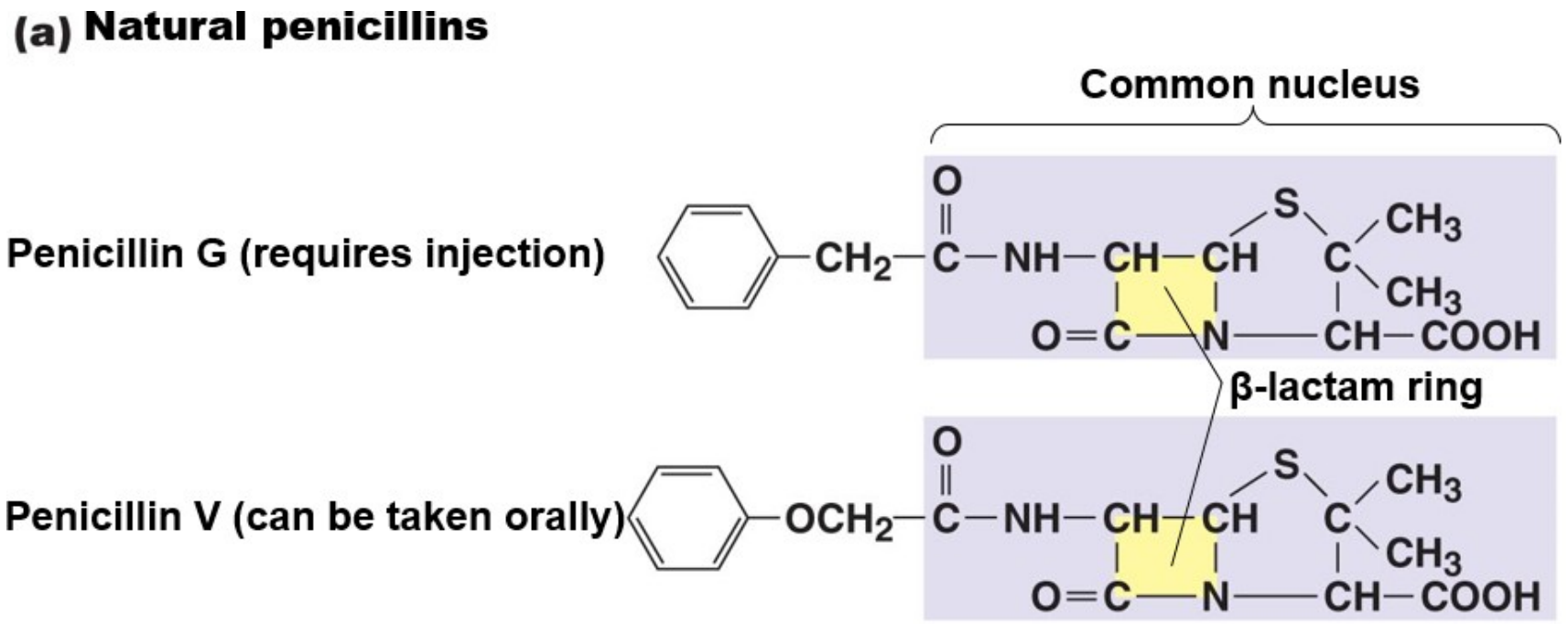


Figure 20.6b The Structure of Penicillins, Antibacterial Antibiotics

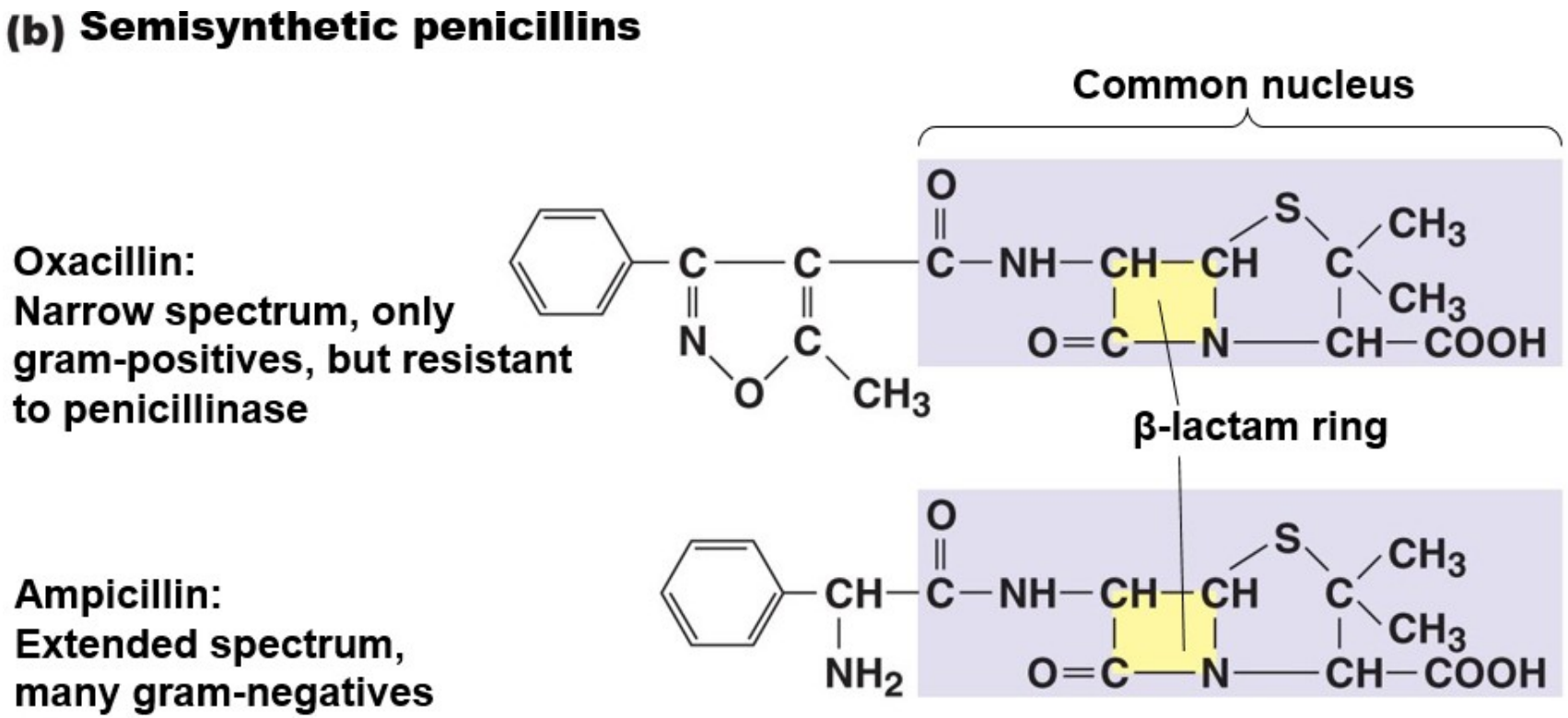


Figure 20.7 Retention of Penicillin G

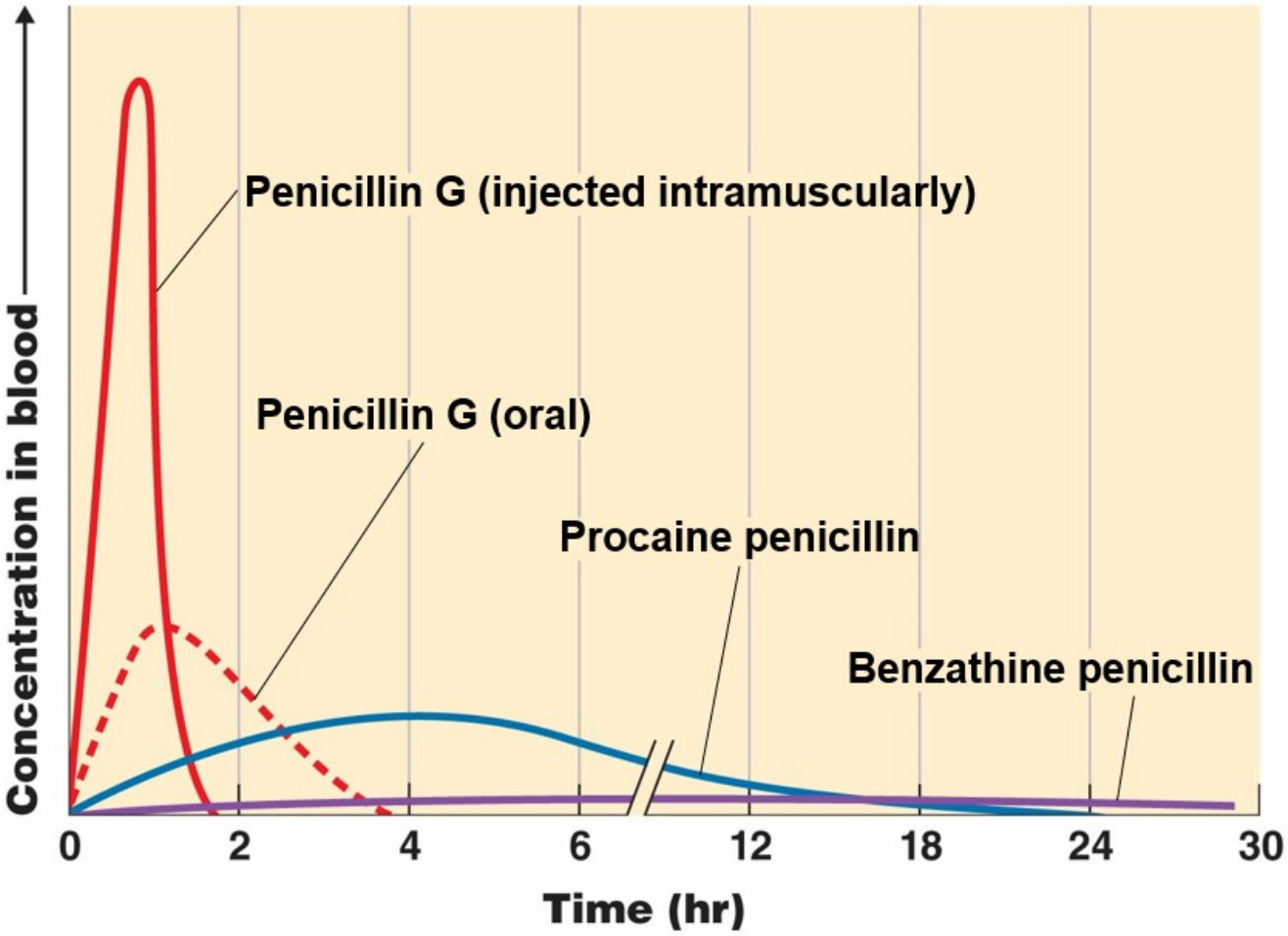
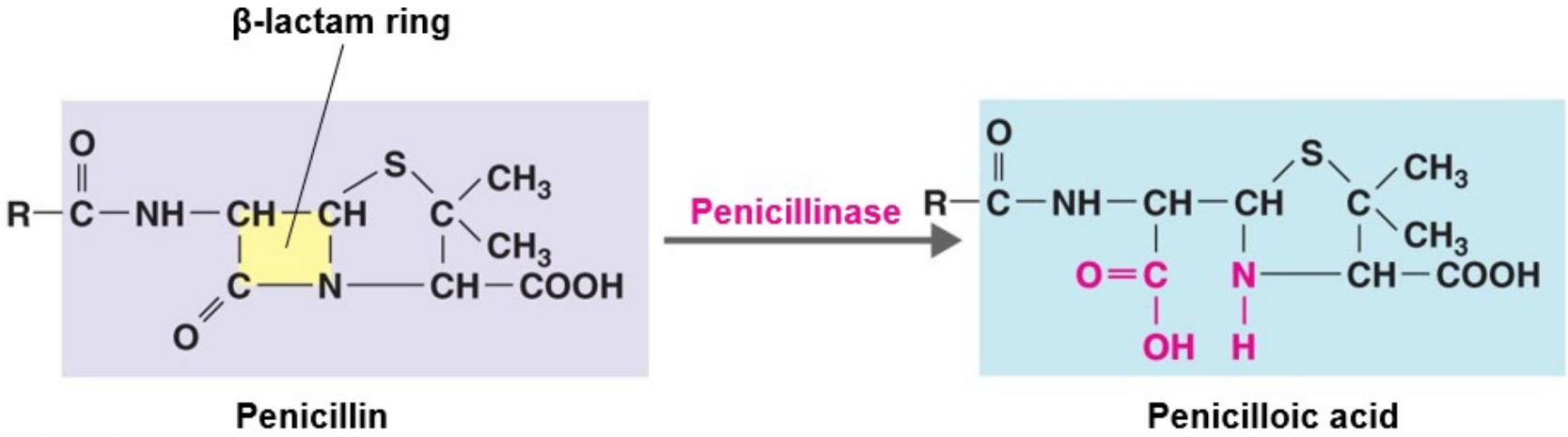


Figure 20.8 The Effect of Penicillinase on Penicillins



Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis
(1 of 3)

- Penicillinase-resistant penicillins
  - Methicillin and oxacillin
- Extended-spectrum penicillins
  - Effective against gram-negatives as well as gram-positives
    - Aminopenicillins: ampicillin, amoxicillin
- Penicillins plus β-lactamase inhibitors
  - Contain clavulanic acid, a noncompetitive inhibitor of penicillinase

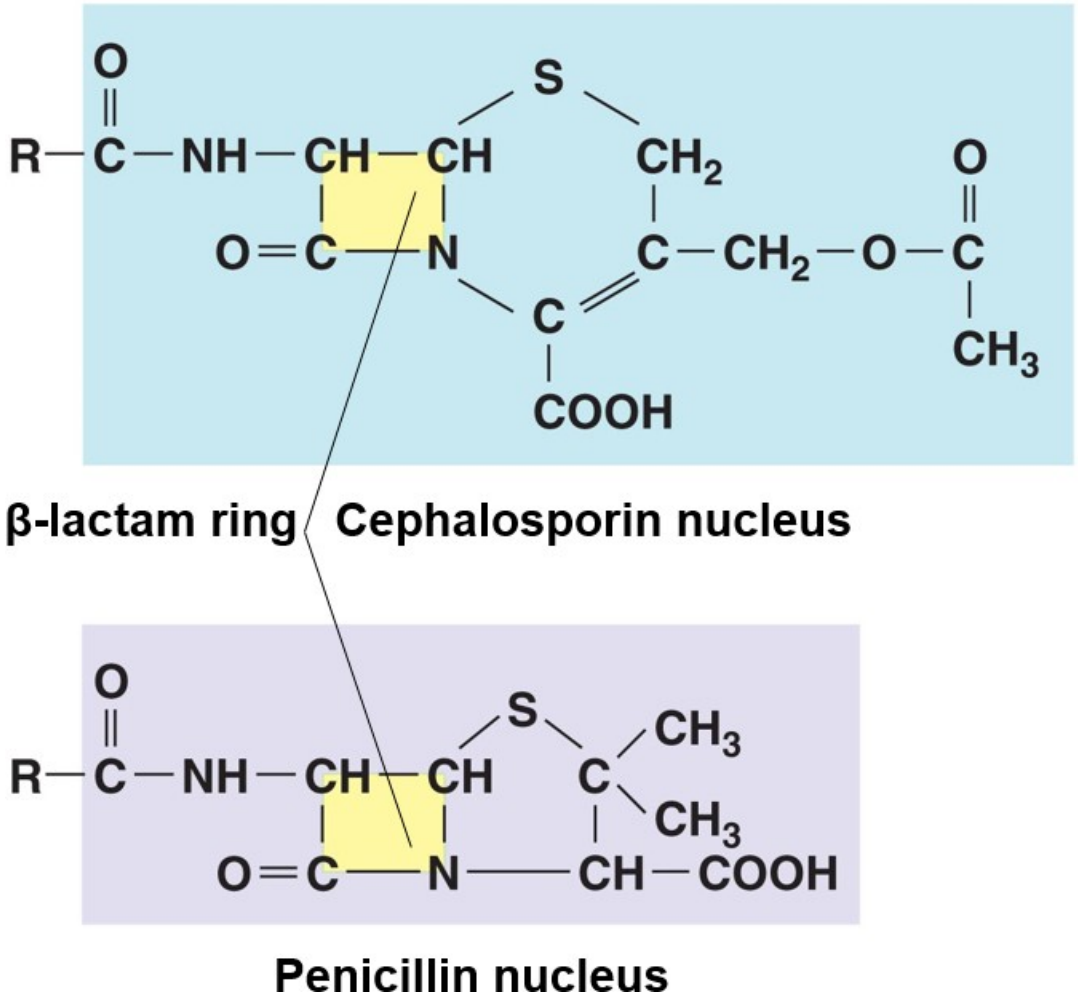
Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis
(2 of 3)

- **Carbapenems**
  - Substitute a C for an S and add a double bond to the penicillin nucleus
  - Broad spectrum
    - Primaxin, doripenem
- **Monobactam**
  - Synthetic; single ring instead of the *β*-lactam double ring
  - Low toxicity; works against only certain gram-negatives
    - Aztreonam

Antibacterial Antibiotics: Inhibitors of Cell Wall Synthesis
(3 of 3)

- **Cephalosporins**
  - Work similar to penicillins
  - β-lactam ring differs from penicillin
  - Grouped according to their generation of development
- Polypeptide antibiotics
  - Bacitracin
    - Topical application; works against gram-positives
  - Vancomycin
    - Glycopeptide
    - Last line against antibiotic-resistant MRSA

Figure 20.9 The Nuclear Structures of Cephalosporin and Penicillin Compared



Antimycobacterial Antibiotics

- **Isoniazid (INH)**
  - Inhibits the mycolic acid synthesis in mycobacteria
- **Ethambutol**
  - Inhibits incorporation of mycolic acid into the cell wall

Check Your Understanding-4

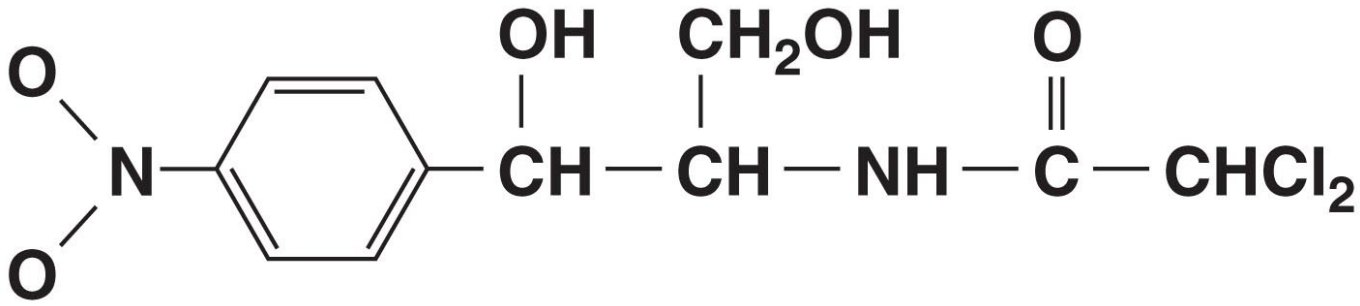
Check Your Understanding

- ✓ One of the most successful groups of antibiotics targets the synthesis of bacterial cell walls; why does the antibiotic not affect the mammalian cell?
  20-6
- ✓ What phenomenon prompted the development of the first semisynthetic antibiotics, such as methicillin?
  20-7
- ✓ What genus of bacteria has mycolic acids in the cell wall?
  20-8

Chloramphenicol

- Inhibits peptide bond formation
  - Binds to the 50S subunit of the 70S ribosome
- Synthesized chemically; broad spectrum
- Can suppress bone marrow and affect blood cell formation

Figure 20.10 The Structure of the Antibacterial Antibiotic Chloramphenicol



Chloramphenicol

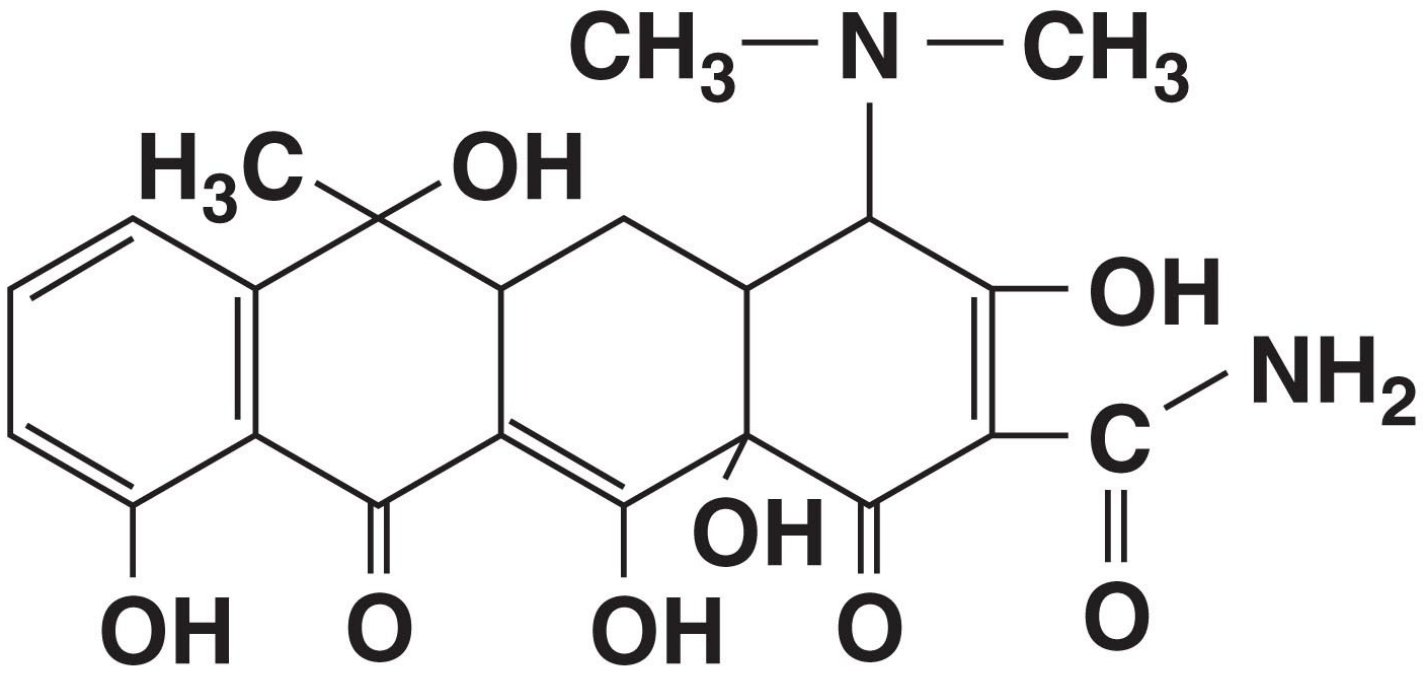
Aminoglycosides

- Amino sugars linked by glycoside bonds
- Change the shape of the 30S subunit of the 70S ribosome
- Can cause auditory damage
- Streptomycin, neomycin, gentamicin

Tetracyclines

- Produced by **Streptomyces** spp.
- Interfere with the tRNA attachment to the ribosome
- Broad spectrum; penetrate tissues, making them valuable against rickettsias and chlamydias
- Can suppress normal intestinal microbiota

Figure 20.11 The Structure of the Antibacterial Antibiotic Tetracycline

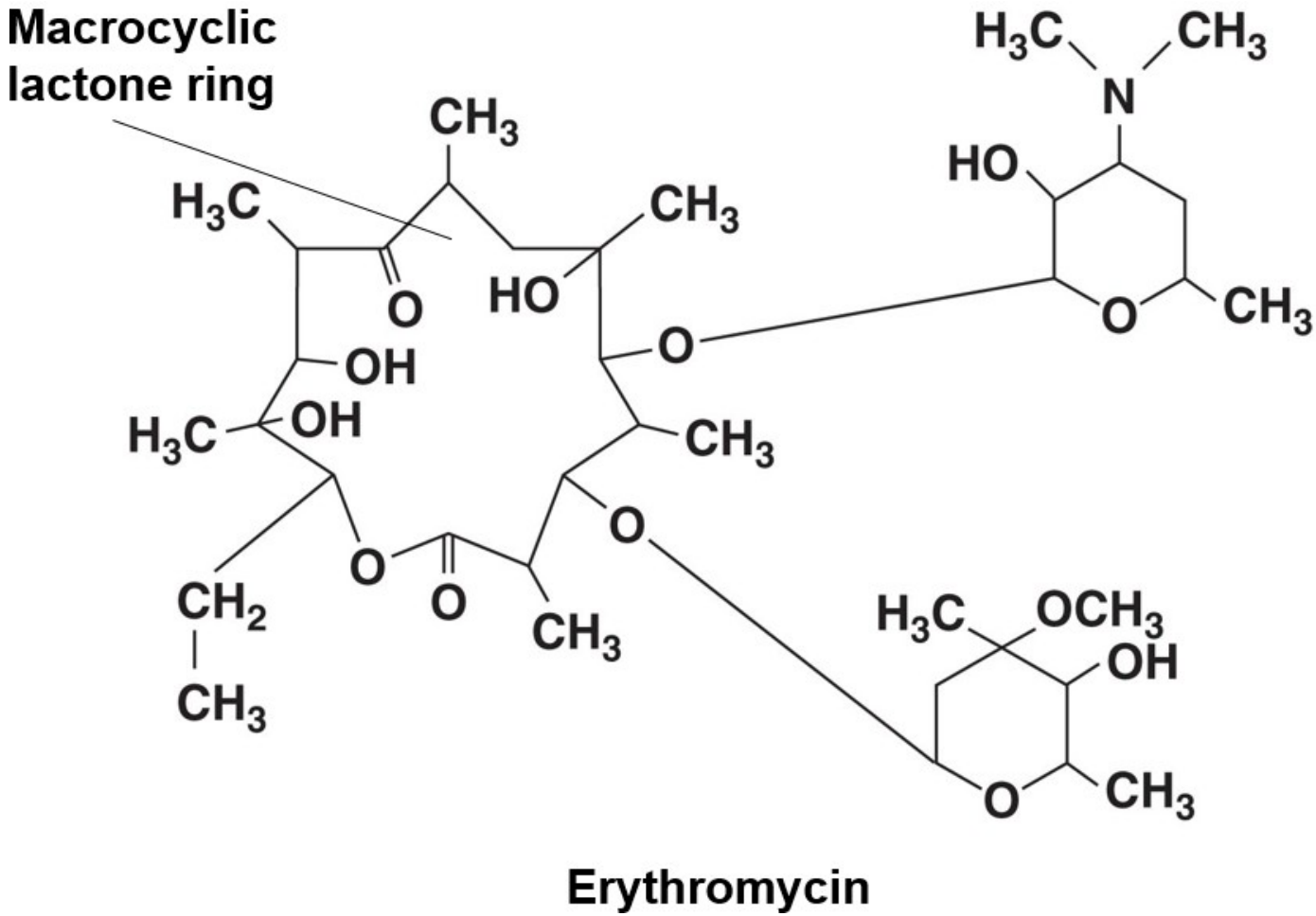


Tetracycline

Inhibitors of Protein Synthesis
(1 of 2)

- **Glycylcyclines**
  - Broad spectrum; bacteriostatic
  - Bind to the 30S ribosomal subunit
  - Inhibits rapid efflux; administered intravenously
  - Useful against MRSA
- **Macrolides**
  - Contain a macrocyclic lactone ring
  - Narrow spectrum against gram-positives
    - Erythromycin

Figure 20.12 The Structure of the Antibacterial Antibiotic Erythromycin, a Representative Macrolide



Erythromycin

Inhibitors of Protein Synthesis
(2 of 2)

- **Streptogramins**
  - Attach to the 50S subunit
  - Work against gram-positives that are resistant to other antibiotics
- Oxazolidinones
  - Bind to the 50S/30S subunit interface
  - Synthetic; combat MRSA (linezolid)
- Pleuromutilins
  - Retapamulin: topical and effective against gram-positives

Check Your Understanding-5

Check Your Understanding

- ✓ Why does erythromycin, a macrolide antibiotic, have activity limited largely to gram-positive bacteria even though its mode of action is similar to that of the broad-spectrum tetracyclines?
  20-9

Injury to the Plasma Membrane

- Affects synthesis of bacterial plasma membranes
- **Lipopeptide**
  - Daptomycin
    - Produced by streptomycetes; used for skin infections
    - Attacks the bacterial cell membrane
  - Polymyxin B
    - Topical; bacteriocidal; effective against gram-negatives
    - Combined with bacitracin and neomycin in nonprescription ointments

Check Your Understanding-6

Check Your Understanding

- ✓ Of the three drugs often found in over-the-counter antiseptic creams—polymyxin B, bacitracin, and neomycin—which has a mode of action most similar to that of penicillin? 20-10

Nucleic Acid Synthesis Inhibitors

- **Rifamycin**
  - Inhibits mRNA synthesis
  - Penetrates tissues; antitubercular activity
- **Quinolone** and **fluoroquinolones**
  - Nalidixic acid
    - Synthetic; inhibits DNA gyrase
  - Norfloxacin and ciprofloxacin
    - Broad spectrum; relatively nontoxic

Check Your Understanding-7

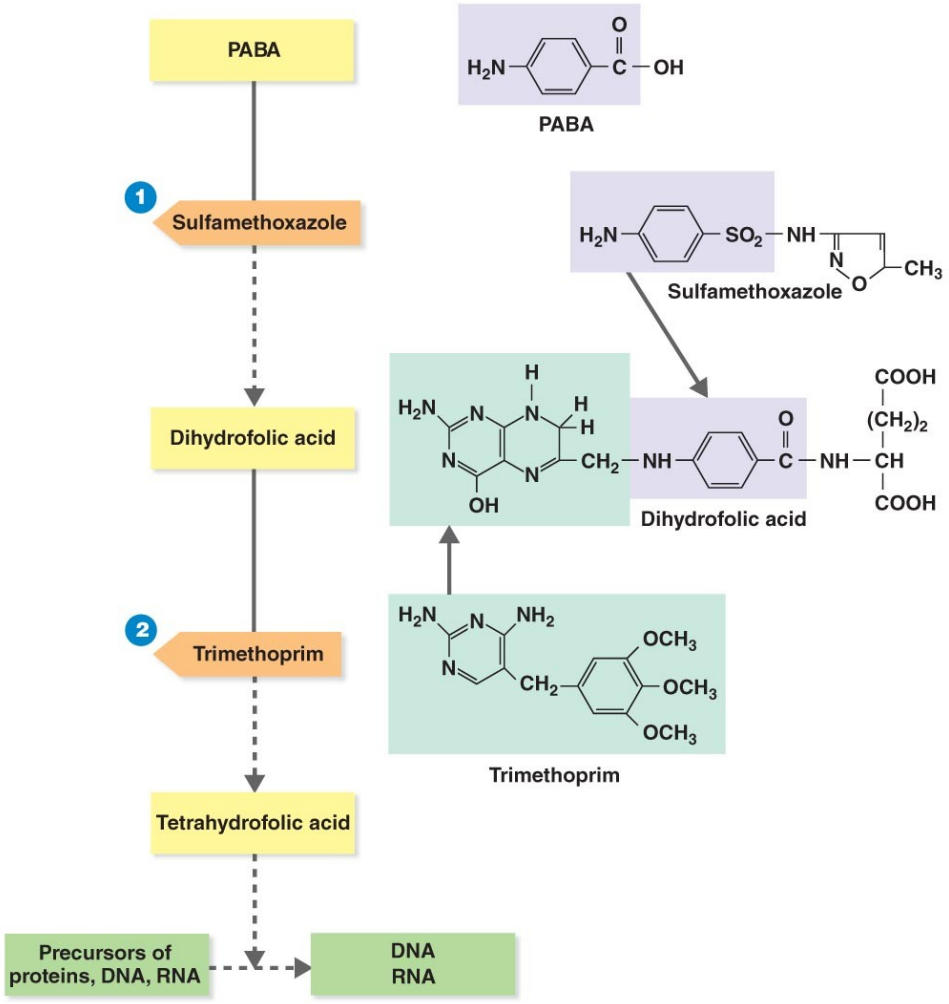
Check Your Understanding

- ✓ What group of antibiotics interferes with the DNA-replicating enzyme DNA gyrase?
  20-11

Sulfonamides

- Inhibit the folic acid synthesis needed for nucleic acid and protein synthesis
- Competitively bind to the enzyme for PABA production, a folic acid precursor
- Combination of trimethoprim and sulfamethoxazole (TMP-SMZ) is an example of drug **synergism**

Figure 20.13 Actions of the Antibacterial Synthetics Trimethoprim and Sulfamethoxazole



Pearson

Check Your Understanding-8

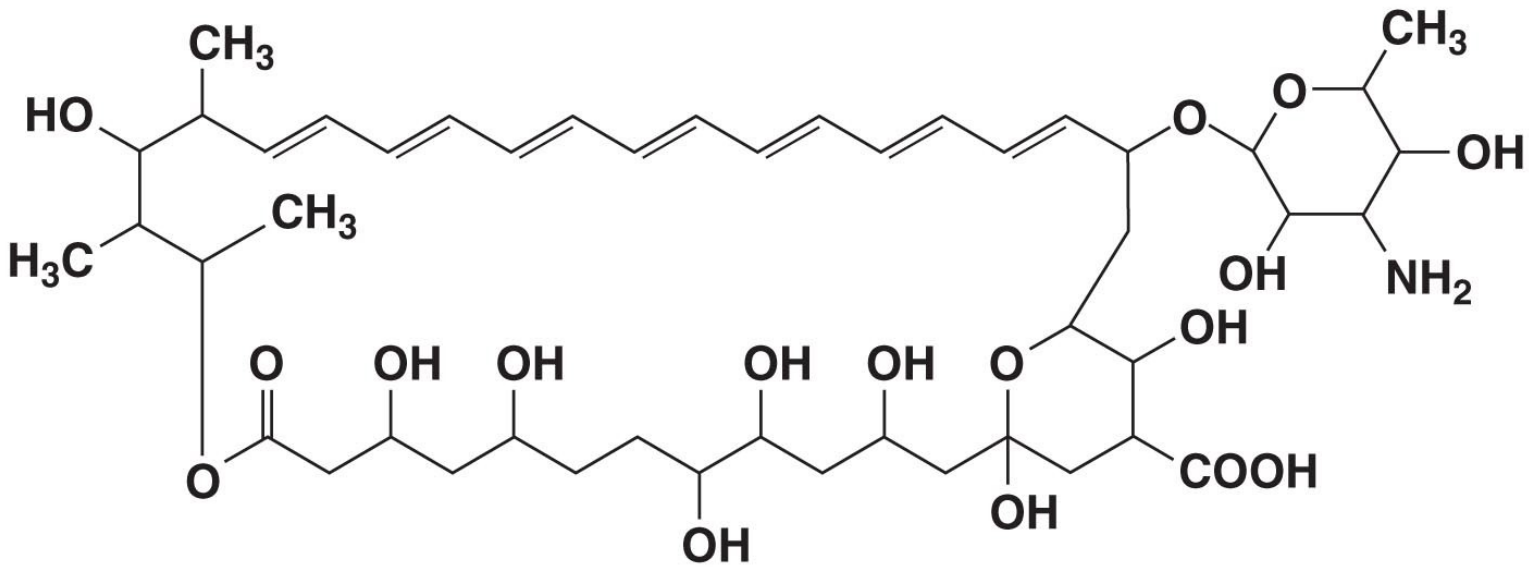
Check Your Understanding

- ✓ Both humans and bacteria need PABA to make folic acid, so why do sulfa drugs adversly impact only bacterial cells?
  20-12

Antifungal Drugs

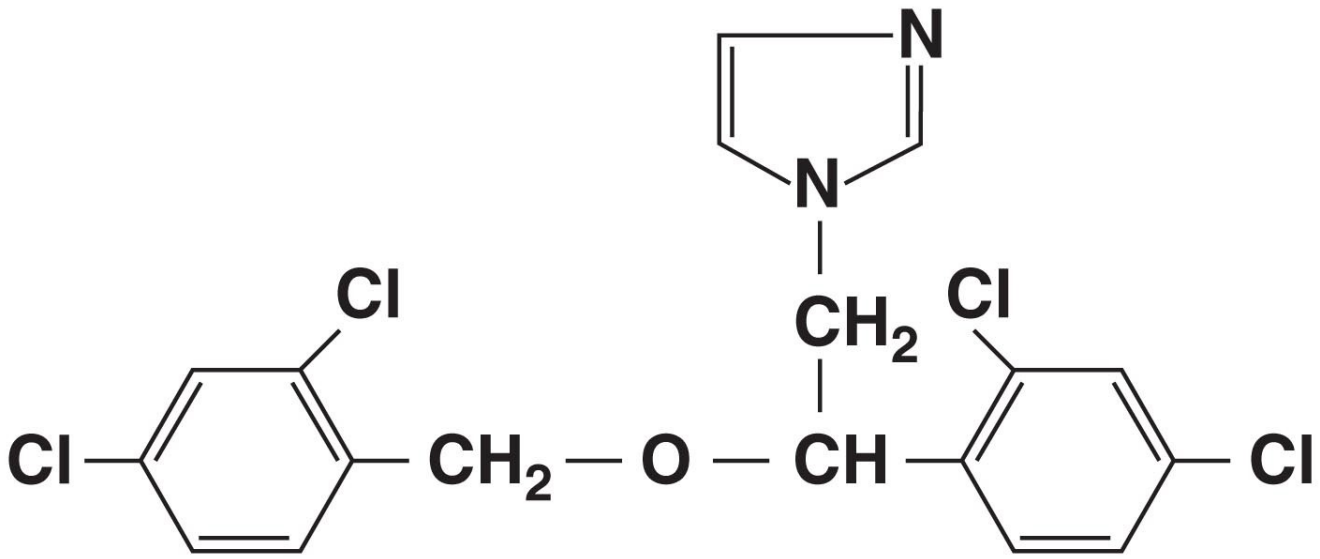
- Agents affecting fungal sterols
  - Interrupt the synthesis of ergosterol, making the membrane excessively permeable
  - Polyenes
    - Amphotericin B: produced by **Streptomyces;** toxic to the kidneys
  - Azoles
    - **Imidazoles:** topical; treat cutaneous mycoses
    - **Triazole:** treat systemic fungal infections
  - **Allylamines**
    - For azole-resistant infections

Figure 20.14 The Structure of the Antifungal Drug Amphotericin B, Representative of the Polyenes



Amphotericin B

Figure 20.15 The Structure of the Antifungal Drug Miconazole, Representative of the Imidazoles



Miconazole

Antifungal Drugs (1 of 2)

- Agents affecting fungal cell walls
  - **Echinocandins**
    - Inhibit the synthesis of β-glucan
- Agents inhibiting nucleic acids
  - Flucytosine
    - Cytosine analog interferes with RNA synthesis

Antifungal Drugs (2 of 2)

- Griseofulvin
  - Produced by **Penicillium**
  - Inhibits microtubule formation
  - Active against superficial dermatophytes
- Tolnaftate
  - For athlete's foot
- Pentamidine
  - Anti-**Pneumocystis**; may bind to DNA

Check Your Understanding-9

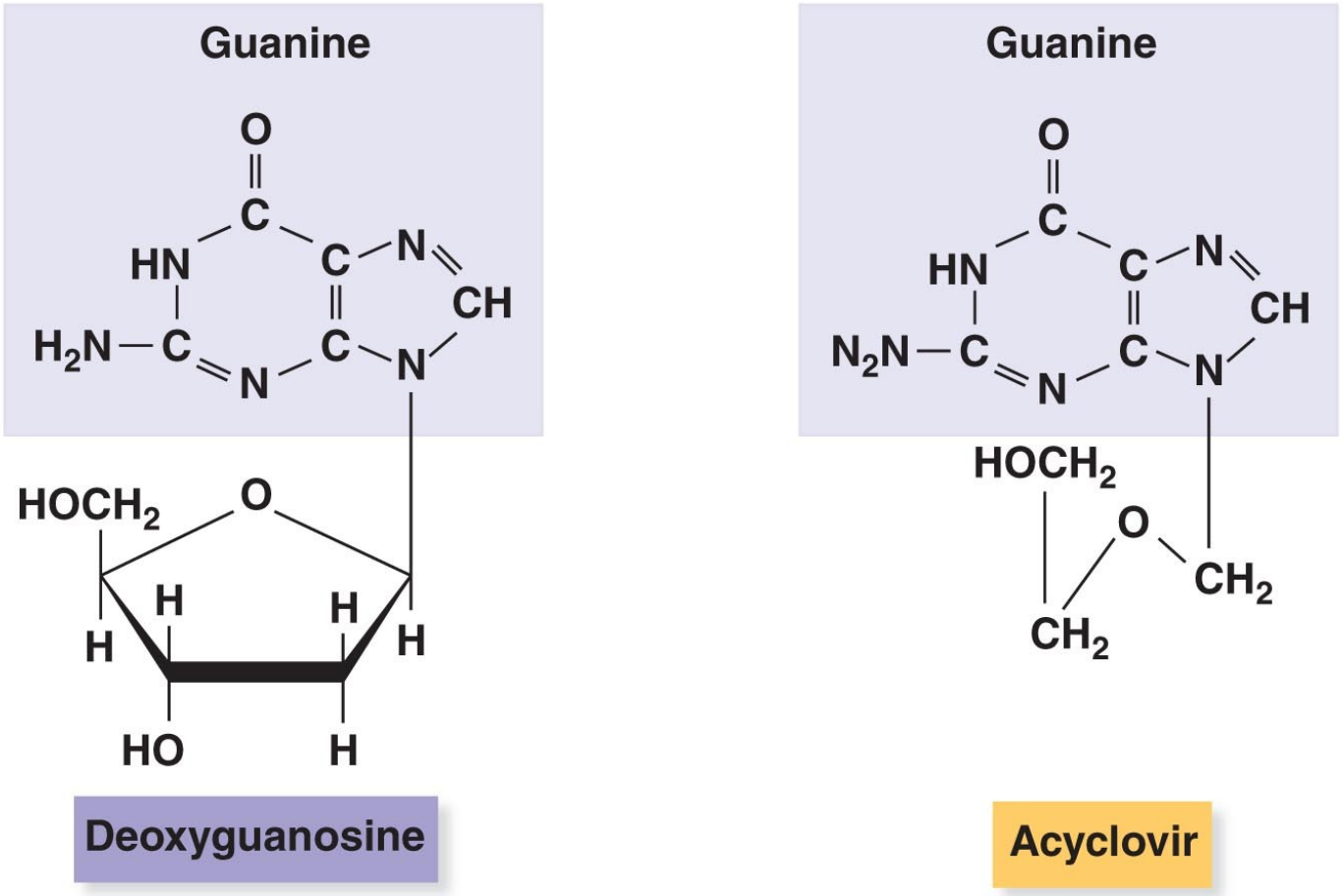
Check Your Understanding

- ✓ What sterol in the cell membrane of fungi is the most common target for antifungal action?
  20-13

Antiviral Drugs (1 of 2)

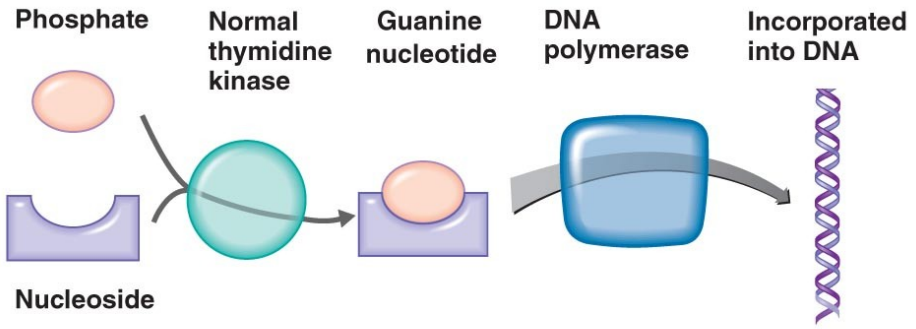
- Entry and fusion inhibitors
  - Block the receptors on the host cell that bind to the virus
  - Block fusion of the virus and cell
- Uncoating, genome integration, and nucleic acid synthesis inhibitors
  - Prevent viral uncoating
  - Inhibit viral DNA integration into the host genome
  - Nucleoside analogs inhibit RNA or DNA synthesis

Figure 20.16a The Structure and Function of the Antiviral Drug Acyclovir

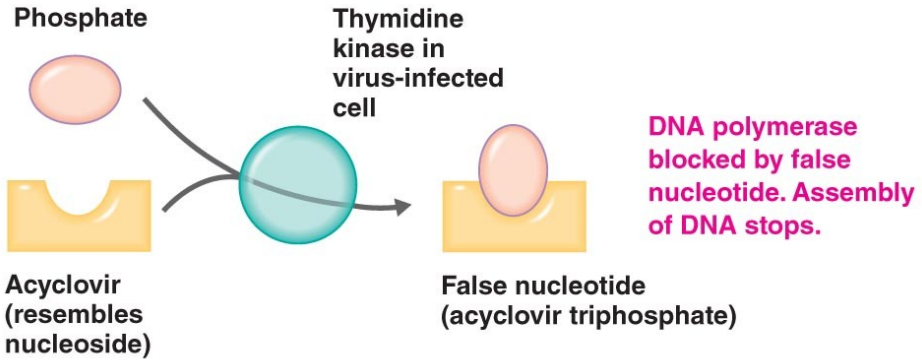


(a) Acyclovir structurally resembles the nucleoside deoxyguanosine.

Figure 20.16b-C The Structure and Function of the Antiviral Drug Acyclovir



(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.



(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) to a false nucleotide, which blocks DNA synthesis by DNA polymerase.

Antiviral Drugs (2 of 2)

- Interference with assembly and release of viral particles
  - **Protease inhibitors**
    - Block the cleavage of protein precursors
- Exit inhibitors
  - Inhibit neuraminidase, an enzyme required for some viruses to bud from the host cell

Interferons

- Produced by viral-infected cells to inhibit further spread of the infection
- Imiquimod
  - Promotes interferon production

Check Your Understanding-10

Check Your Understanding

- ✓ One of the most widely used antivirals, acyclovir, inhibits the synthesis of DNA. Humans also synthesize DNA, so why is the drug still useful in treating viral infections?
  20-14

Antivirals for Treating HIV/AIDS

- **Antiretroviral**
  - **Nucleoside analog** (zidovudine)
  - **Nucleotide analog** (tenofovir)
  - **Non-nucleoside inhibitors** (nevirapine)
  - Protease inhibitors (atazanavir)
  - Integrase inhibitors (raltegravir)
  - Entry inhibitors (miraviroc)
  - Fusion inhibitors (enfuvirtide)

Antiprotozoan and Antihelminthic Drugs (1 of 2)

- Antiprotozoan drugs
  - Quinine and chloroquine
    - Treat malaria
  - Artemisinin
    - Kills **Plasmodium** that causes malaria
  - Metronidazole (Flagyl)
    - Also interferes with anaerobic bacteria
    - Treats **Trichomonas,** giardiasis, and amebic dysentery

Antiprotozoan and Antihelminthic Drugs (2 of 2)

- Antihelminthic drugs
  - Niclosamide
    - Prevents ATP production
      - Treats tapeworms
  - Praziquantel
    - Alters membrane permeability
      - Treats tapeworms and flukes
  - Mebendazole and albendazole
    - Interfere with nutrient absorption
      - Treat intestinal helminths
  - Ivermectin
    - Paralysis of helminths
      - Treats roundworms and mites

Check Your Understanding-11

Check Your Understanding

- ✓ What was the first drug for parasitic infections? 20-15

Tests to Guide Chemotherapy

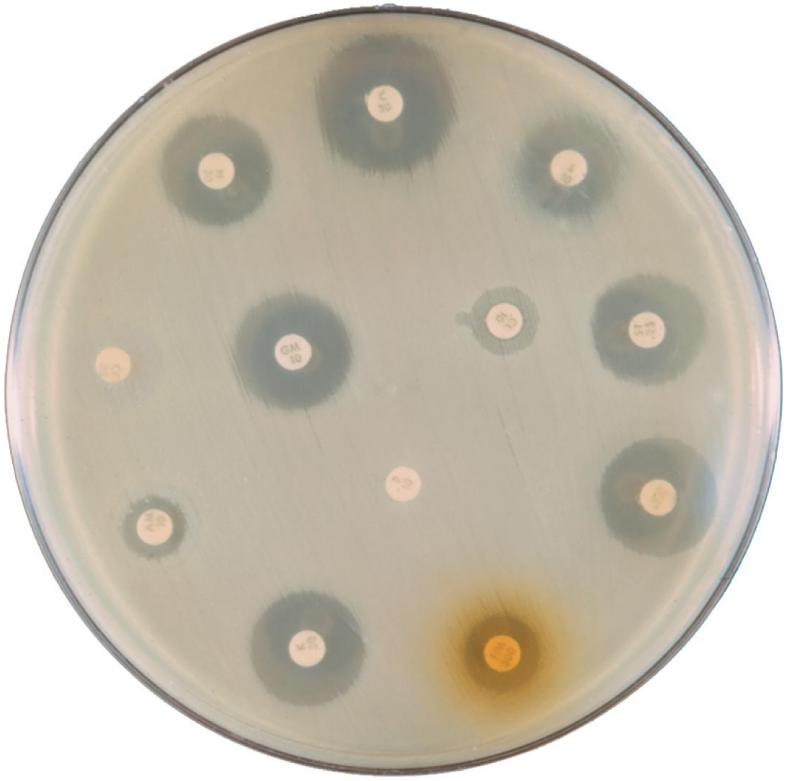
Learning Objective

20-16 Describe two tests for microbial susceptibility to chemotherapeutic agents.

The Diffusion Methods (1 of 2)

- **Disk-diffusion method** (Kirby-Bauer test)
  - Tests the effectiveness of chemotherapeutic agents
    - Paper disks with a chemotherapeutic agent are placed on agar containing the test organism
    - **Zone of inhibition** around the disk determines the sensitivity of the organism to the antibiotic

Figure 20.17 The Disk-Diffusion Method for Determining the Activity of Antimicrobials

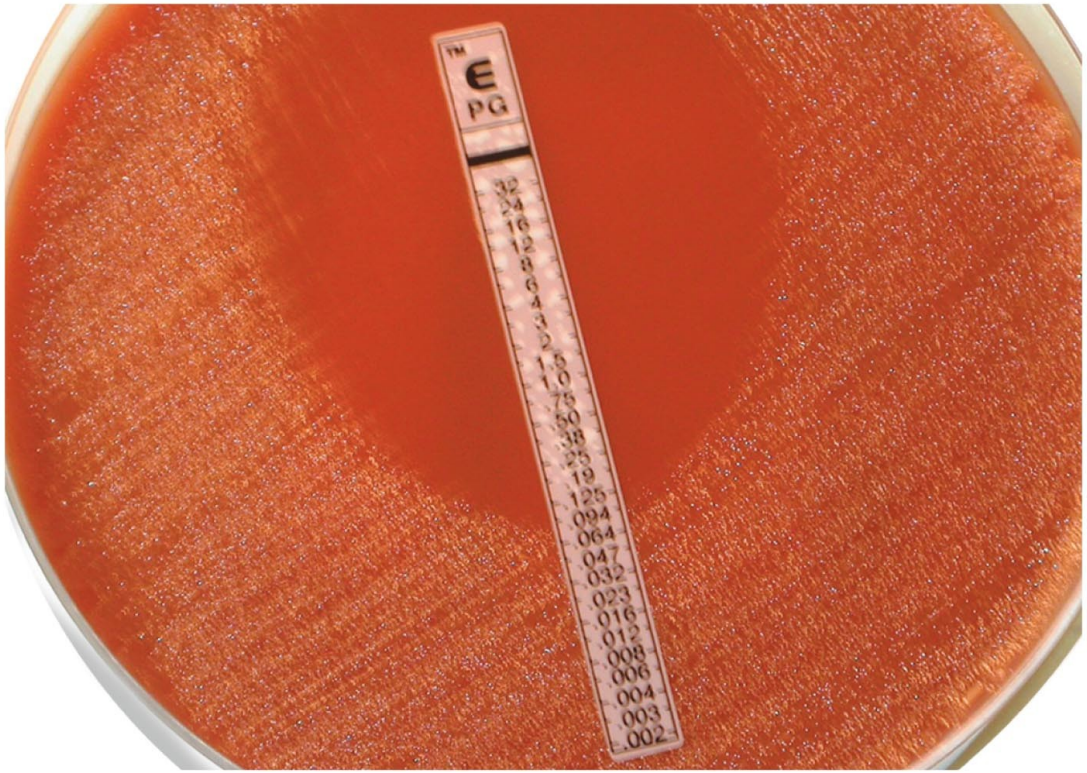


The Diffusion Methods (2 of 2)

- **E test**
  - Determines the **minimal inhibitory concentration (MIC)**
    - Lowest antibiotic concentration preventing bacterial growth

Figure 20.18 the E Test (for Epsilometer)

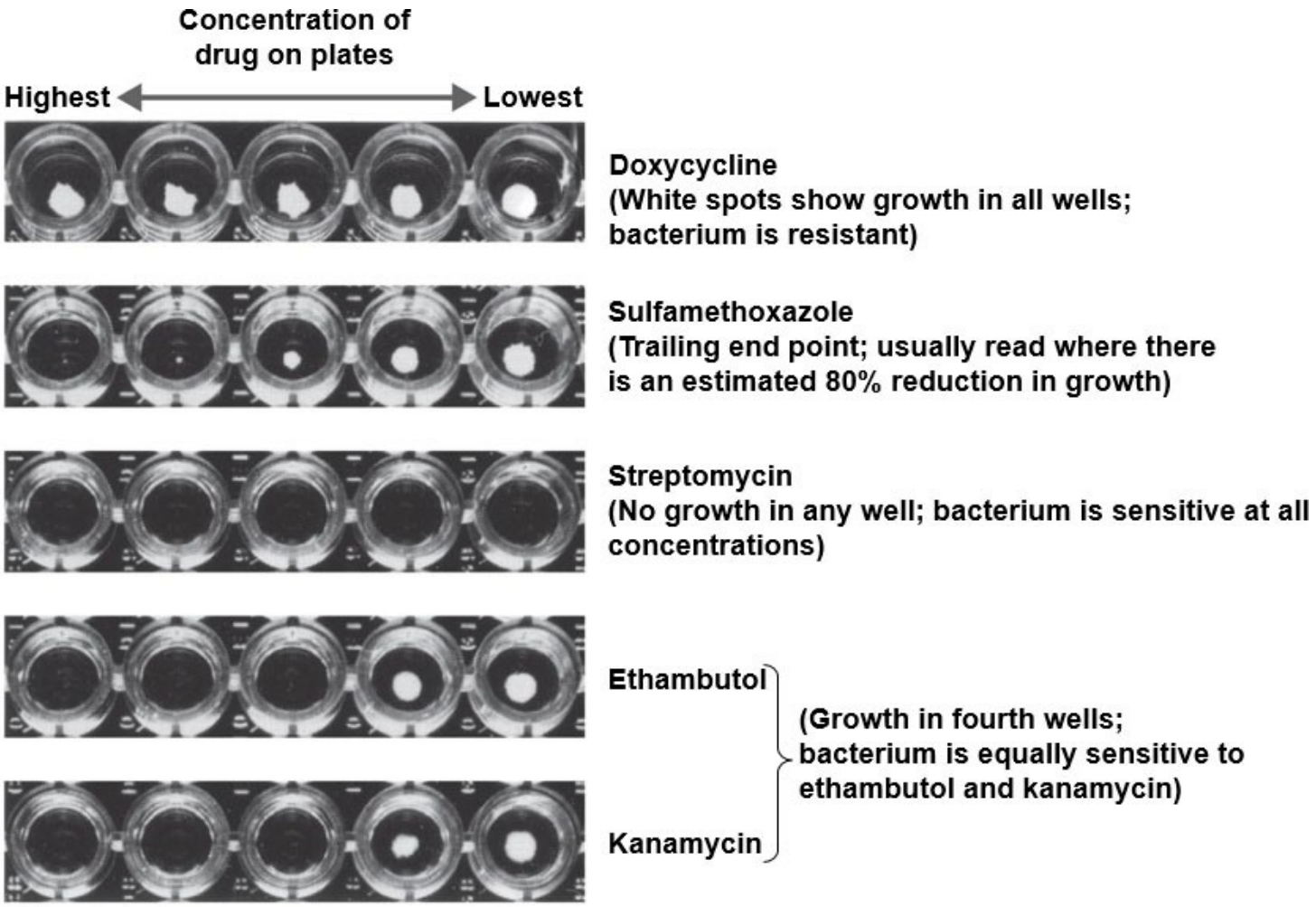
The E test (for epsilometer), a gradient diffusion method that determines antibiotic sensitivity and estimates minimal inhibitory concentration (MIC).



Broth Dilution Tests

- Determine the MIC and **minimal bactericidal concentration (MBC)** of an antimicrobial drug
- Test organism is placed into the wells of a tray containing dilutions of a drug; growth is determined
- **Antibiograms**
  - Reports that record the susceptibility of organisms encountered clinically

Microtiter, Plate Used for Testing for Minimal Inhibitory Concentration (MIC) of Antibiotics



Check Your Understanding-12

Check Your Understanding

- ✓ In the disk-diffusion test, the zone of inhibition indicating sensitivity around the disk varies with the antibiotic. Why?
  20-16

Resistance to Antimicrobial Drugs (1 of 2)

Learning Objective

20-17 Describe the mechanisms of drug resistance.

Resistance to Antimicrobial Drugs (2 of 2)

- **Persister cells:** microbes with genetic characteristics allowing for their survival when exposed to an antibiotic
- **Superbugs:** bacteria that are resistant to large numbers of antibiotics
- Resistance genes are often spread horizontally among bacteria on plasmids or transposons via conjugation or transduction

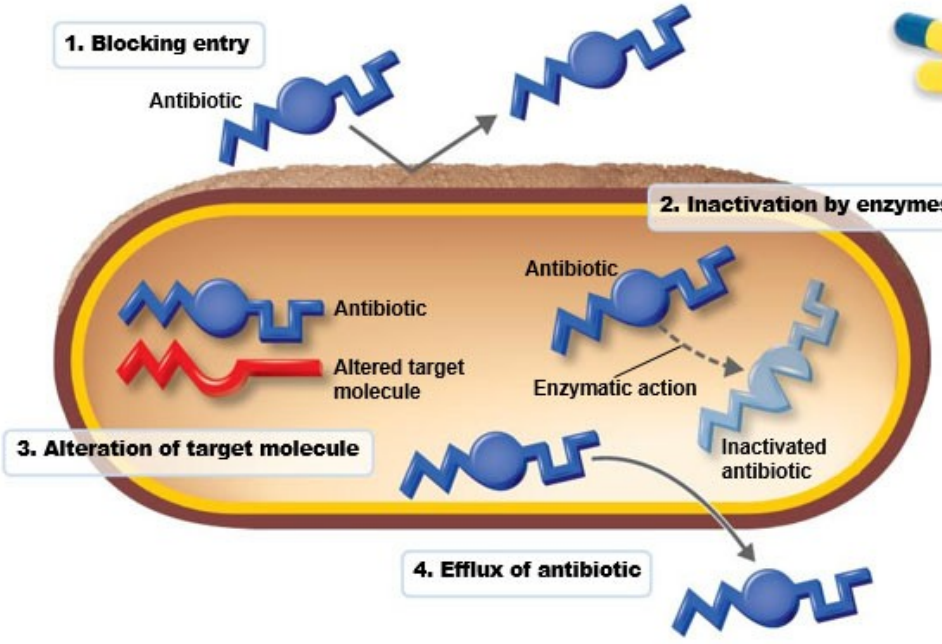
Antibiotic Resistance: Origins of Resistance

PLAY **Animation: Antibiotic Resistance: Origins of Resistance**

Mechanisms of Resistance

- Enzymatic destruction or inactivation of the drug
- Prevention of penetration to the target site within the microbe
- Alteration of the drug's target site
- Rapid efflux (ejection) of the antibiotic
- Variations of mechanisms of resistance

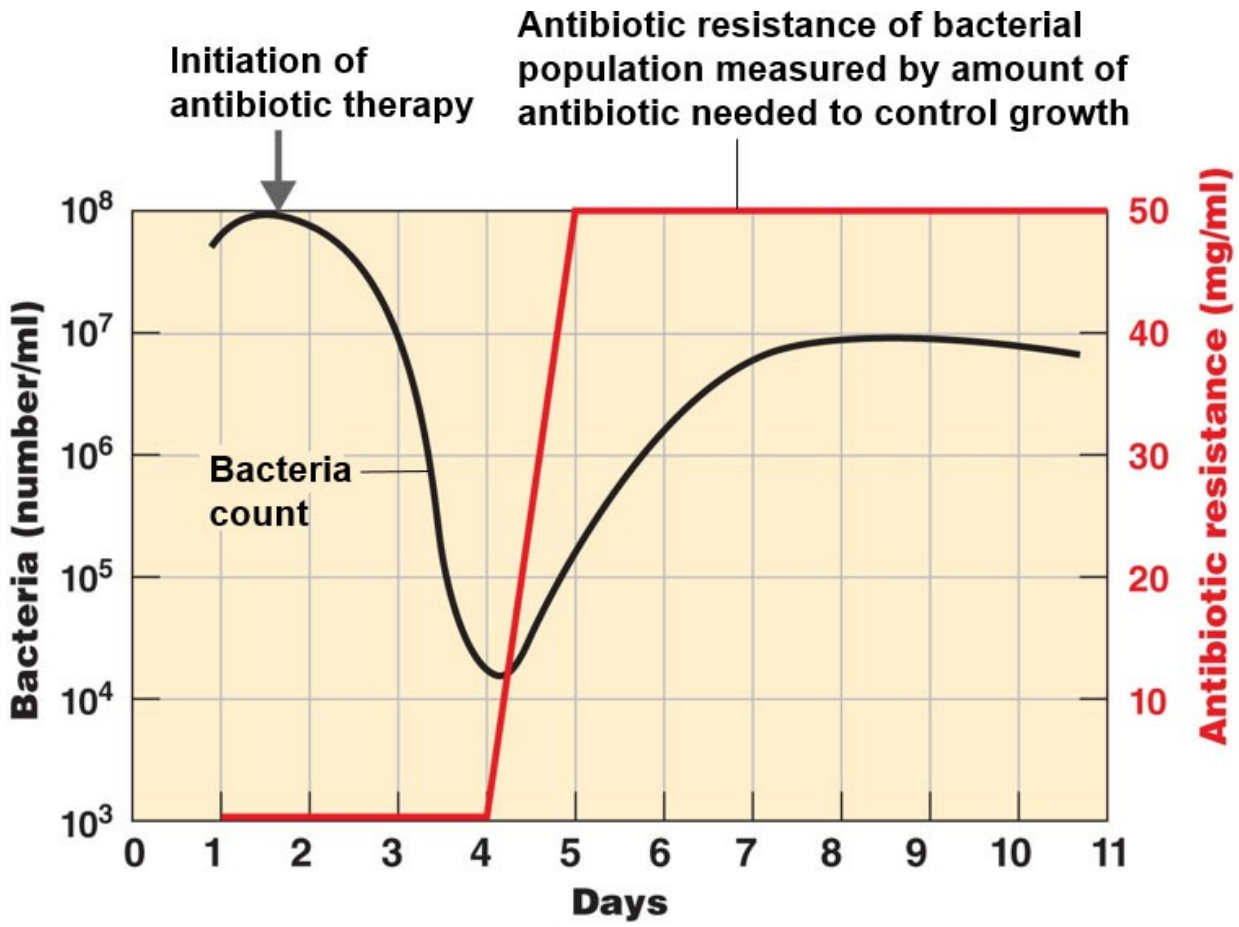
Figure 20.20 Bacterial Resistance to Antibiotics



KEY CONCEPTS

- There are only a few mechanisms of microbial resistance to antimicrobial agents: blocking the drug's entry into the cell, inactivation of the drug by enzymes, alteration of the drug's target site, efflux of the drug from the cell, or alteration of the metabolic pathways of the host.
- The mechanisms of bacterial resistance to antibiotics are limited. Knowledge of these mechanisms is critical for understanding the limitations of antibiotic use.

Figure 20.21 The Development of an Antibiotic-Resistant Mutant During Antibiotic Therapy



Antibiotic Resistance: Forms of Resistance

PLAY **Animation: Antibiotic Resistance: Forms of Resistance**

Antibiotic Misuse

- Misuse of antibiotics selected for resistance mutants
- Misuse includes:
  - Using outdated or weakened antibiotics
  - Using antibiotics for the common cold and other inappropriate conditions
  - Using antibiotics in animal feed
  - Failing to complete the prescribed regimen
  - Using someone else's leftover prescription

Check Your Understanding-13

Check Your Understanding

- ✓ What is the most common mechanism that a bacterium uses to resist the effects of penicillin?

  20-17

Antibiotic Safety

- Therapeutic index: risk versus benefit
- Reactions of antibiotics with other drugs
- Damage to organs
- Risk to the fetus

Effects of Combinations of Drugs (1 of 2)

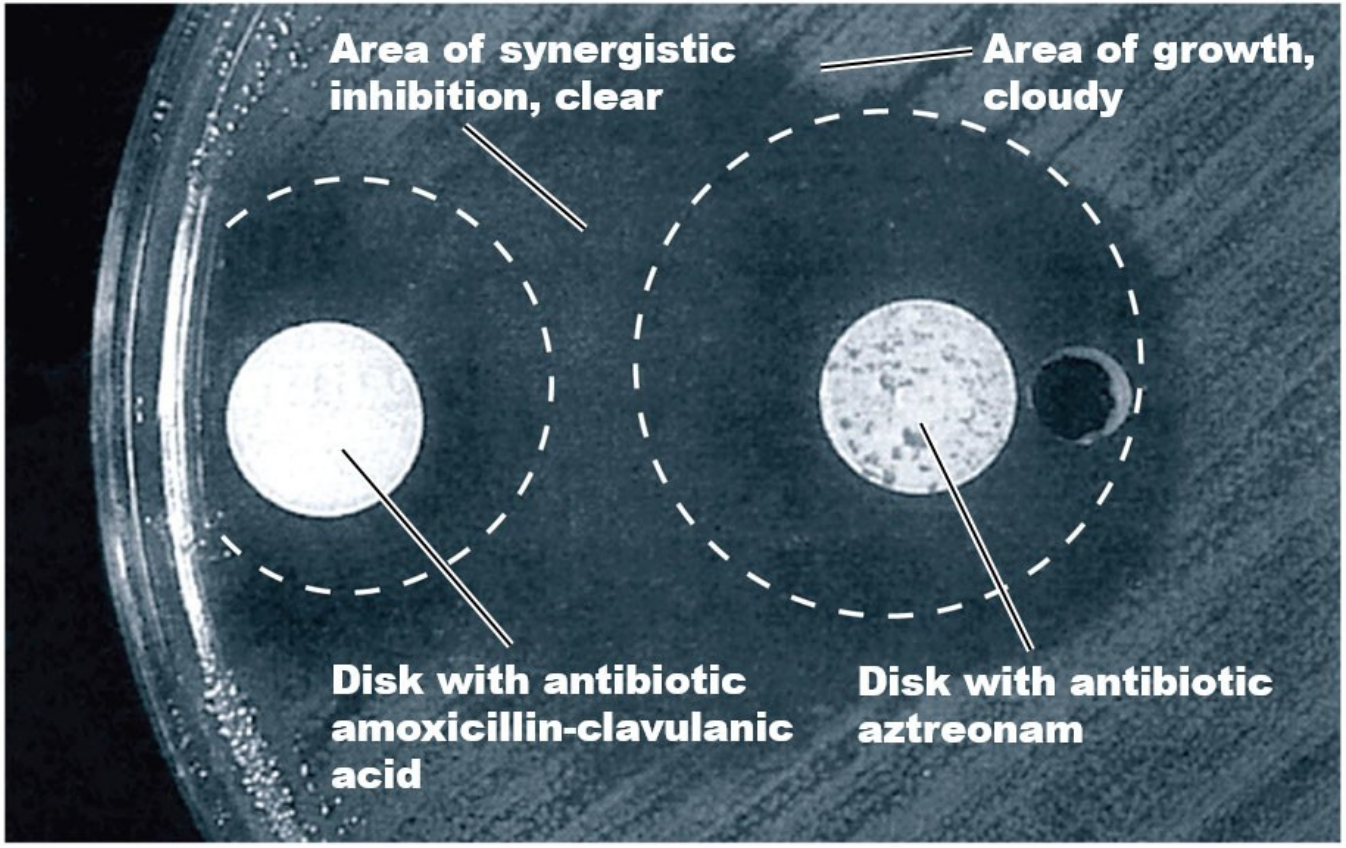
Learning Objective

20-18 Compare and contrast synergism and antagonism.

Effects of Combinations of Drugs (2 of 2)

- **Synergism:** the effect of two drugs together is greater than the effect of either alone
- **Antagonism:** the effect of two drugs together is less than the effect of either alone

Figure 20.23 An Example of Synergism Between Two Different Antibiotics



Pearson

Check Your Understanding-14

Check Your Understanding

- ✓ Tetracycline sometimes interferes with the activity of penicillin. How?
  20-18

Future of Chemotherapeutic Agents (1 of 2)

Learning Objective

20-19 Name three areas of research on new chemotherapeutic agents.

Future of Chemotherapeutic Agents (2 of 2)

- Target virulence factors
- Sequester iron, which feeds pathogens
- Antimicrobial peptides produced by various organisms
- Phage therapy
- Bacteriocins: antimicrobial peptides produced by bacteria

Check Your Understanding-15

Check Your Understanding

- ✓ What are defensins? (**Hint:** See Chapter 16.)
  20-19